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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/682,199	10/10/2003	Peter Hermentin	06478.1495	1253

22852 7590 07/09/2010

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ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
07/09/2010	PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte PETER HERMENTIN, THOMAS CUESTA-LINKER, and KARL-HEINZ SCHMIDT

Appeal 2009-015014
Application 10/682,199
Technology Center 1600

Before ERIC GRIMES, DONALD E. ADAMS, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 involving claims to a method for analyzing multimer-forming proteins by gel electrophoresis. The

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

STATEMENT OF THE CASE

Claims 16-25, 27-28, 30-31, 33, and 35 are on appeal. Claims 16 and 25 are representative and read as follows:

16. A method for the determination of multimers of multimer-forming proteins by gel electrophoresis, comprising

fractionating a sample containing von Willebrand factor or fibrinogen into multimer bands by submarine electrophoresis in agarose gel, wherein the agarose gel is continuous, homogeneous and free of lumps,

visualizing multimer bands by a dye in the gel, and

optionally quantifying the dyed multimer bands.

25. [The method of claim 16,] wherein the gel electrophoresis is carried out at temperatures between 8°C and 12°C.

The claims stand rejected under 35 U.S.C. § 103(a) as follows:

- claims 16-24, 27-28, 30-31, 33 and 35 in view of Shainoff[2] and Bhat;[3] and
- claim 25 in view of Shainoff, Bhat and Perrella.[4]

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[2] J. R. Shainoff, *Electrophoresis and Direct Immunoprobing on Glyoxyl Agarose and Polyacrylamide Composites*, in A. Charmbach et al. (eds.) 6 ADVANCES IN ELECTROPHORESIS 61-177, VCH (New York), 1993.

[3] S. P. Bhat et al., *Use of "Submarine" Gel Electrophoresis for Running Multiple Two-Dimensional Protein Gels,* 170 ANAL. BIOCHEM. 105-109 (1988).

[4] M. Perrella et al., *Low-Temperature Electrophoresis Methods,* 259 METHODS IN ENZYMOL. 468-487 (1995).

I.

Issue

The Examiner has rejected claims 16-24, 27-28, 30-31, 33 and 35 under 35 U.S.C. § 103(a) as Shainoff and Bhat. The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner finds that Shainoff discloses fractionating von Willebrand factor multimers by continuous, homogeneous agarose gel electrophoresis (Ans. 3), as well as "visualizing multimer bands by a dye in the gel" (*id.* at 4). The Examiner finds that Bhat discloses "the use of 'submarine' electrophoresis for resolving proteins" (*id.*). The Examiner concludes that it "would have been obvious for a person of ordinary skill in the art to replace the electrophoretic protocol of Shainoff with a 'submarine' method because Bhat ... discovered that the 'submarine' method allows for stacking of multiple gels allowing for multiple simultaneous runs" (*id.*).

Appellants contend that the cited references would not suggest the method of claim 16 because Shainoff describes a variety of electrophoresis procedures and thus requires picking and choosing to arrive at the invention of claim 16 (Appeal Br. 9-10). Appellants also contend that Shainoff discloses a gel made of glyoxyl agarose, not an agarose gel as claimed (*id.* at 11-12), and that Bhat "is directed to an entirely different electrophoresis procedure" that involves two-dimensional protein electrophoresis and polyacrylamide gels (*id.* at 13).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Shainoff and Bhat would have made obvious a method meeting the limitations of claim 16?

Findings of Fact

1. Shainoff discloses the development of glyoxyl agarose gels for "direct immunoprobing, because of need to analyze fibrinogen derivatives that were virtually completely resistant to blot-transfer" (Shainoff, 66).

2. Shainoff discloses that a "2% gel has been found useful for separating von Willebrand factor multimers" (*id.* at 78).

3. Shainoff discloses that a commercially available product comprises a mixture of glyoxyl agarose and regular agarose (*id.* at 72).

4. Shainoff discloses that the gels may be continuous (*id.* at 75).

5. Shainoff discloses protein staining of glyoxyl agarose gels with Coomassie Blue (*id.* at 98).

6. Bhat discloses that "[a]n apparatus commonly used for the electrophoresis of submerged agarose gels was used to separate proteins.... The units for submerged horizontal gel electrophoresis are easily made or are inexpensively available commercially." (Bhat, abstract.)

Analysis

Claim 16 is directed to a method for determining multimers of von Willebrand factor or fibrinogen by fractionating a sample into multimer bands by submarine agarose gel electrophoresis and visualizing multimer bands using a dye.

Shainoff discloses a method for fractionating von Willebrand factor multimers, among other things, by glyoxyl agarose gel electrophoresis in a continuous gel system. Shainoff also discloses visualizing proteins in a gel using a dye. Shainoff does not specifically disclose using submarine gel electrophoresis, but Bhat discloses that submerged, or submarine, agarose gels were commonly used in the art to separate proteins. In view of these

disclosures, it would have been obvious to one of skill in the art to carry out Shainoff's electrophoretic fractionation using submarine gel electrophoresis because Bhat discloses that submarine gel electrophoresis was commonly used with agarose gels.

Appellants contend that Shainoff is a review article that describes a variety of electrophoresis procedures and thus requires using hindsight to pick and choose from the disclosed element in order to arrive the invention of claim 16 (Appeal Br. 9-10). Appellants further contend that Shainoff discloses a preference for immunoprobing of the gels rather than dye staining (Reply Br. 4).

This argument is not persuasive. Although Shainoff does provide a number of options for protein separation and visualization, it discloses that continuous agarose gels were conventional for separating proteins and dye staining was conventional for visualizing them. It also discloses that glyoxyl agarose gels were known for separating fibrinogen derivatives and von Willebrand factor multimers. Appellants have provided no persuasive reason for concluding that combining these conventional elements would not have been obvious. Although Shainoff discloses that immunostaining provides "greater sensitivity and intensity of staining" (Shainoff 79, legend to Fig. 4), it shows that dye staining is also effective for visualizing fibrinogen in a gel (*id.* at Fig. 4). Appellants have pointed to no evidence showing that dye staining would not be effective for visualizing multimers of fibrinogen or von Willebrand factor.

Appellants also contend that Shainoff does not suggest regular agarose alone, as opposed to glyoxyl agarose (Appeal Br. 8-9; Reply Br. 3).

This argument is not persuasive. During examination, claim terms are to be given the broadest reasonable interpretation consistent with the specification. The Specification does not define the term "agarose" to exclude agarose derivatives. Thus, the broadest reasonable interpretation of the term encompasses a derivatized agarose such as glyoxyl agarose, and the blend of agarose and derivatized agarose disclosed in Shainoff.

Finally, Appellants argue that one of skill in the art would not have been motivated to combine the cited references because Bhat "is directed to an entirely different electrophoresis procedure" that involves two-dimensional protein electrophoresis and polyacrylamide gels (Appeal Br. 13).

This argument is not persuasive. Shainoff discloses agarose gel electrophoresis and Bhat discloses that a submerged gel (submarine gel) apparatus is commonly used for agarose gel electrophoresis. The fact that Bhat also discloses an additional use for a submarine gel apparatus does not detract from the obviousness of combining Bhat's submarine electrophoresis method with Shainoff's agarose gel.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that Shainoff and Bhat would have made obvious a method meeting the limitations of claim 16.

II.

Issue

The Examiner has rejected claim 25 under 35 U.S.C. § 103(a) as being obvious in view of Shainoff, Bhat and Perrella.

The Examiner relies on Shainoff and Bhat as discussed above. The Examiner finds that Perrella discloses "the use of temperature to modify electrophoresis" (Ans. 5) and concludes that it would have been obvious to modify the electrophoretic method suggested by Shainoff and Bhat "by modifying temperature because Perrella ... teach[es] that the use of temperature to modify electrophoresis allows for probing of 'intermediate stages of ligation' and 'quaternary structural changes'" (*id.*).

Appellants contend that Perrella would not suggest a temperature range of 8°C to 12°C because Perrella discusses the electrophoresis of hemoglobin in a polyacrylamide gel system "at temperatures below the freezing point of water using cryosolvents" and thus would not have suggested the optimization of electrophoresis of a different protein in a different gel system (Appeal Br. 14-15).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the cited references would have made it obvious to carry out the electrophoresis suggested by Shainoff and Bhat at a temperature between 8°C and 12°C?

Additional Findings of Fact

7. Perrella discloses that "[s]tudies of hemoglobin at intermediate stages of ligation are difficult because of the mobility of the heme ligands, which reversibly associate and dissociate from the subunits, and the ligation-linked reversible dissociation of the hemoglobin tetramers into uncooperative dimers" (Perrella, 469).

8. Perrella discloses "cryogenic quenching and electrophoresis techniques to analyze mixtures of species in a partial state of ligation either at equilibrium or under dynamic conditions" (*id.* at 469-470).

9. Perrella discloses that a

> breakthrough in cryogenic electrophoresis was achieved by the use of copolymers of acrylamide and methyl or ethyl acrylate. ... Electrophoretic separations of hemoglobin hybrids have been carried out at -45°.... However, because the mobility of hemoglobin during the approach to focusing equilibrium is low, isoelectric focusing is usually carried out at -25°.

(*Id.* at 472.)

Analysis

Claim 25 is directed to the method of claim 16, wherein the gel electrophoresis is carried out at temperatures between 8°C and 12°C. The Examiner finds that Perrella suggests optimizing the temperature of the electrophoresis suggested by Shainoff and Bhat.

Appellants argue that Perrella's "electrophoresis of hemoglobin in copolymers of acrylamide and methyl or ethyl acrylate at temperatures below the freezing point of water using cryosolvents" would not have suggested carrying out agarose gel electrophoresis of von Willebrand factor or fibrinogen at 8°C to 12°C (Appeal Br. 14-15).

Appellants' arguments are persuasive. Perrella discusses the electrophoretic fractionation of hemoglobin, rather than von Willebrand factor or fibrinogen, in a gel system that is different from that used by Shainoff and Bhat, and at significantly different temperatures than those required by claim 25. The Examiner has not adequately explained why Perrella would have made obvious the temperature range recited in claim 25.

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that the cited references would have made it obvious to carry out the

electrophoresis suggested by Shainoff and Bhat at a temperature of 8°C to 12°C.

SUMMARY

We affirm the rejection of claims 16-24, 27-28, 30-31, 33 and 35 under 35 U.S.C. § 103(a). However, we reverse the rejection of claim 25 under 35 U.S.C. § 103(a).

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

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